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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/559,783 | 12/08/2005 | Mitsuko Kosaka | 64614(70904) | 1080 |

21874 7590 03/13/2007
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| EXAMINER | |
|---|---|
| DUTT, ADITI | |
| ART UNIT | PAPER NUMBER |
| 1649 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/13/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/559,783 | KOSAKA, MITSUKO | |
| | Examiner | Art Unit | |
| | Aditi Dutt | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/18/06,8/1/06,1/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

1. The amendment of 8 December 2005 has been entered in full. Claims 4, 5, 7,10, 12 and 14 are amended.

### *Election/Restrictions*

2 Applicant's election without traverse of Group I, represented by claims 1-11, drawn to a method for producing tissue cells culturing iris pigment epithelial cells and obtaining pluripotent cells therefrom, in the reply filed on 16 January 2007 is acknowledged.

3. Claims 12-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 16 January 2007.

4. Claims 1-11, drawn to a method for producing tissue cells culturing iris pigment epithelial cells and obtaining pluripotent cells therefrom, are under consideration in the instant application.

### *Drawings*

5. The instant drawings do not comply with 37 C.F.R. § 1.84(U)(1), which states that partial views of a drawing which are intended to form one complete

view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. Figures 2, 3 and 6 of the instant application, for example, are presented on two or more separate panels, which are labeled "FIG 2(a), 2(b)...."; "FIG 3(a), 3(b)" and "FIG 6(a), FIG 6(b)", in the instant specification should be renumbered as "FIG "2A 2B...3A, 3B..., 6A, 6B", respectively. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly.

6. Additionally, although Figure 2 has 5 panels, only three are labeled as FIG 2(a), 2(b) and 2(c). Two panels are not labeled. Appropriate correction is required

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 5 and 6 are rejected as being vague and indefinite because, the meaning of the term "tissue-restoring" cannot be ascertained. It is not clear whether the term "restoring" denotes one of the following processes, viz. "maintaining, culturing, stabilizing, preserving...etc.". The metes and bounds of

the recitation cannot be determined from the claim or instant specification, as filed.

9. Claim 1 is rejected, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: an additional step indicating the culturing conditions for obtaining tissue cells.

10. Claims 2-4, 7-11 are indefinite for being dependent from indefinite claims.

***Claim Rejections - 35 USC § 112-Scope of Enablement***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing stem cells expressing Oct-3/4 and cardiac genes GATA4 and Nkx2.5, by selectively culturing iris pigment epithelial cells, does not reasonably provide enablement for a method for producing pluripotent cells that are tridermic differentiable from the iris pigment epithelial cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

13. The claims are drawn to a method for producing tissue cells comprising: (i) obtaining iris pigment epithelial cells from an eyeball of a postnatal animal, for

example, chicken, mouse, rat or human, by enzyme treatment (claims 1-3, 5-6); (ii) culturing epithelial cells by floated coagulated mass culturing technique to obtain pluripotent stem cells, that are Oct-3/4 positive, and/or tridermic differentiable (claims 1, 4). The claims further require that the differentiation inducing conditions comprise, culture of the cells in the presence of serum (fetal calf or avian) with a growth factor (FGF or EGF) (claims 7-11).

14. The specification of the instant application teaches that the iris pigment epithelial cells are obtained from the eyeball of a chick, followed by selective culturing of the cells using the (neurosphere) method of floated coagulated mass culture (Example1, pages 18-20). The specification further teaches the differentiation of the iris derived cells under various differentiation inducing culture conditions, and suggests, that the cells can differentiate into all types of tridermic tissues (Example 2, page 21, para 2). Furthermore, the specification using 11 days and 3-month old rats (page 22, Example 3), demonstrates the expression of Oct-3/4 gene in the iris tissue (Figures 6A and 6B), and of myocardial genes in the differentiated cells (Figure 4B). However, the specification does not teach any methods or working examples to indicate that all possible tissues representing the tridermic cell types could be generated from the iris pigment epithelial cells. Undue experimentation would be required of a skilled artisan to determine such. The instant specification as filed, fails to provide enough guidance for one skilled in the art on how to practice the instant invention, thereby requiring undue experimentation to discover how to use Applicant's invention, as currently claimed.

15. The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands,* 8 USPQ2d, 1400 (CAFC 1988).

16. Relevant literature teaches that the retinal pigment epithelium from rats in the early embryonic stages, can transdifferentiate in vitro to neural retina (Zhao et al. Brain Res 677: 300-310, 1995, figure 3). The art also teaches pigmented epithelial cells from the dorsal iris of various animals, including aged humans, can differentiate to form lens tissue in vitro (Tsonis, P. Differentiation 70: 397-409, 2002; page 399, column 2, para 2). However, the relevant literature, does not teach that iris pigment epithelial cells can produce stem cells that are tridermic differentiable.

17. Furthermore, with regards to the differentiation of stem cells to other tissue types, results are inconsistent, and subject to improved culture conditions to obtain a population of highly purified stem cells. For example, the art teaches that embryonic stem cells can spontaneously differentiate into cardiac myocyte like cells, and by a "default pathway for differentiation" to neural precursor cells (Stem cell Information. The NIH resource for stem cell research, Chapter 3, pages 1-11; page 8, para 3). The art also teaches that, although the Oct-3/4 gene is a marker of undifferentiated embryonic stem cells, the expression level of the gene

determines the actual differentiation into various tissues, and that a critical level of the gene is necessary for maintaining the self-renewal and differentiation properties of the embryonic stem cells (Friel et al. Adv Drug Del Rev 57: 1894-1903, 2005; page 1898, para 2). Friel et al. further teach that the expression of Oct-3/4 alone "is not sufficient to maintain pluripotency" of the embryonic stem cells, but additionally requires the cytokine induced action (page 1899, column 1, para 1). Still further, the art based on transdifferentiation and somatic stem cell plasticity studies, cautions that experiments employing purified adult stem cell populations while eliciting 'reprogramming of stem cell genomes', might also involve the occurrence of "rare transformation events and cell fusion with host cells" that needs to be resolved (Hawley and Sobieski, Stem Cells 20: 195-197, 2002; page 197, concluding para). Based on the unpredictability of success and variation in the results, as seen from the prior and post art literature, undue experimentation would be required of the skilled artisan to develop a method for producing tissue cells that are tridermic differentiable using post natal iris pigment epithelial cells, with a reasonable expectation of success. There is little guidance in the specification regarding what other tissues are generated (besides cardiac cells).

18. Due to the large quantity of experimentation necessary for generating tissue cells belonging to all three germinal layers, from the postnatal iris pigment epithelial cells; the lack of direction/guidance presented in the specification; the complex nature of the invention; the unpredictability of generating all tissue cells;

undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

***Claim Rejections - 35 USC § 112, first paragraph- Written Description***

19. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. The claims are drawn to a method for producing tissue cells comprising: (i) obtaining iris pigment epithelial cells from an eyeball of a postnatal animal, for example, chicken, mouse, rat or human, by enzyme treatment (claims 1-3, 5-6); (ii) culturing epithelial cells by floated coagulated mass culturing technique to obtain pluripotent stem cells, that are Oct-3/4 positive, and/or tridermic differentiable (claims 1, 4). The claims further teach that the differentiation inducing conditions comprise, culture of the cells in the presence of serum (fetal calf or avian) with a growth factor (FGF or EGF) (claims 7-11).

21. The specification of the instant application teaches that the iris pigment epithelial cells are obtained from the eyeball of a chick, followed by selective culturing of the cells using the (neurosphere) method of floated coagulated mass culture (Example1, pages 18-20). The specification further teaches the

differentiation of the iris derived cells under various differentiation inducing culture conditions, and suggests that the cells differentiated into all the types of tridermic tissues (Example 2, page 21, para 2). Furthermore, the specification demonstrates the expression of Oct-3/4 gene in the iris tissue (Figures 6A and 6B), from 11 days and 3-month old rats (page 22, Example 3), as well as the expression of myocardial genes in the differentiated cells (Figure 4B). However, the brief description in the specification of one example of mesodermal cells (cardiac myocytes), one example of ectodermal cells (iris), does not provide adequate written description of an entire genus of tissues and cells that are tridermic differentiable. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of specific physiological characteristics, physical and/or chemical properties, functional features, structure/function correlation, or any combination thereof. However, in this case, the specification has not shown a relationship between the claimed genus of tridermic differentiable stem cells, derived from the iris pigment epithelial cells.

22. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the

art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

23. The skilled artisan cannot envision the entire genus of tridermic differentiable stem cells, of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

25. Therefore, only methods of generation of cardiac myocytes and iris, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

### *Claim Rejections - 35 USC § 103*

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 1-11, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosaka et al. (Exp Cell Res 245: 245-251, 1998), and Haruta et al., (Nat Neurosc 4: 1163-1164, 2001); in view of Reynolds and Weiss (Sc. 255: 1707-1710, 1992).

29. The claims are drawn to a method for producing tissue cells comprising: (i) obtaining iris pigment epithelial cells from an eyeball of a postnatal animal, for example, chicken, mouse, rat or human, by enzyme treatment (claims 1-3, 5-6); (ii) culturing epithelial cells by floated coagulated mass culturing technique to obtain pluripotent stem cells, that are Oct-3/4 positive, and/or tridermic differentiable (claim 1, 4). The claims further specify that the differentiation inducing conditions comprise culture of the cells in the presence of serum (fetal calf or avian) with a growth factor (FGF or EGF) (claims 7-11).

30. Kosaka et al. teach the removal of eyeballs from 1 day old (postnatal) chicken, thereafter isolating the pigmented epithelial cells from the iris into a

single cell suspension after treatment with 0.1% trypsin in PBS (page 246, column 1, "Preparation of cell"). Kosaka et al. further teach the growth of the iris derived pigmented epithelial cells in culture for 18 days before reaching confluency. The depigmented iris pigment epithelial cells are harvested and cultured for transdifferentiation to lens tissue (page 246, column 1, "Procedure for cell culture").

31. Kosaka et al. do not teach culture conditions necessary for differentiation.

32. Haruta et al. teach the differentiation of iris-derived cells (from adult rats) to rod photoreceptor (page 1163, column 2, para 1), in response to *Crx* gene transfer. Haruta et al. further teach the differentiation inducing culture conditions comprising culturing in the presence of 1% fetal bovine serum with 10ng/ml FGF, as growth factor.

33. Kosaka et al. and Haruta et al. do not teach the culturing of iris pigment epithelium cells by a floated coagulated mass culturing technique.

34. Reynolds and Weiss teach a cell culture method suggestive of the floated coagulated mass culturing technique using neurospheres. The reference teaches the proliferation of cells from adult mouse striatum in a culture system wherein the cells undergo cell division and form clusters, that migrate across the substrate (page 1708, figures 1A-1C; legend to figure 1). The reference further teaches that after 6-8 divisions, the spheres (or clusters) of cells are lifted off the substrate and floated in suspension (page 1708, figure 1D).

35. Kosaka et al., Haruta et al., and Reynolds and Weiss, do not explicitly teach the expression of Oct3/4. However, this limitation will be an inherent feature, since the combined references teach the same culture limitations of the instant application.

36. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of culturing the iris pigment epithelial cells of Kosaka et al. and Haruta et al., to the floated coagulated mass culture technique as taught by Reynolds and Weiss. The person of ordinary skill in the art would have been motivated to use this technique for cell culture and differentiation as this would facilitate the selection of a specific cell type aggregate by antibody immuno-staining (Reynolds and Weiss, page 708, Figure 1E and 1F). The person of ordinary skill in the art would have expected success because the method of floated coagulated mass technique (or neurosphere), was well established and accepted in the art at the time the invention was made.

37. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

## ***Conclusion***

38. No claims are allowed.

39. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Hu et al. Invest Opthal Vis Sc 33: 2443-2453, 1992.

(Reference showing the isolation and culture of human iris pigment epithelial cells).

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

41. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

42. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD

23 February 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER